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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Malmlöf et al. Confirmation No. 5384

Serial No.: 10/772,997 Group Art Unit: 1654

Filed: February 5, 2004 Examiner: Audet, Maury A.

For: Use of a Growth Hormone or a Growth Hormone Secretagogue for Appetite-Suppression or Induction of Satiety

DECLARATION OF DR. KJELL MALMLÖF

Commissioner for Patents
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I, Kjell Malmlöf, Ph.D., hereby state:

1. ***My qualifications.*** I am a Principal Scientist and Group Leader in Diabetes Pharmacology at Novo Nordisk A/S. I have been a scientist at Novo Nordisk since 1996 and have 27 years of experience in scientific research, with an emphasis in the research of peptide hormones, such as growth hormone. I have authored or co-authored over 20 original peer-reviewed research papers in this field (a truncated copy of my *curriculum vitae* is attached hereto).

2. ***Relationship to the subject patent application.*** I am a named inventor in the above-referenced patent application. I am familiar with the claims of the subject patent application and with the rejections made in the Office Action mailed September 18, 2006.

3. ***The obese rats used in the studies in the subject patent application are an effective model for obese human beings with regard to the effect of growth hormone on appetite.*** Mature, obese, female Wistar rats, such as those used in the experiments described in the subject patent application, are a reliable pre-clinical model of how an obese human patient will respond to administration of growth hormone ("GH") in respect of appetite (i.e., such a model may be considered to be very likely predictive of a similar outcome in human patients). In fact, the model has been found to have a general predictability. Compounds like

the cannabinoid receptor antagonist Acomplia® (Rimonabant) and Sibutramine with established inhibitory effects on food intake in humans also reduce food intake in this model (Malmlöf, unpublished observations).

The similarity in the reaction of Wistar rats and humans to growth hormone is widely supported by published literature in the field. For example, peer-reviewed published research papers (including my work) shows that mature, obese, female Wistar rats (such as those used in the experiments described in the subject application), experience an increase in muscle mass, lose fat, and develop hyperinsulinemia when given GH (see reference list appended hereto) [1-3]. Such effects also have been observed in studies where humans (particularly obese humans) have been given GH.

In addition, there are a number of other relevant metabolic similarities between obese Wistar rats and obese humans. For example, compromised GH secretion in rats is associated with obesity [4], as is also seen in humans [5]. Moreover, GH promotes an increase in circulating levels of β-hydroxybutyrate in both humans and rats [1,2]. An increase in this plasma metabolite indicates and increased hepatic lipid oxidation. Also, the enzyme lipoprotein lipase (LPL) that governs the entry of lipids from the circulation into adipose tissue is inhibited in both species [3,4]. These examples all indicate that the response to growth hormone in humans and rats (particularly obese humans and rats) is qualitatively the same. It is for this reason that the Wistar rats used in the experiments described in the subject patent application are a very appropriate model for humans.

4. ***The different effects of growth hormone observed in the literature with respect to mammals, and particularly in rats and humans, can be explained by differences in adiposity or organism studied.*** As pointed out by the Examiner in the most recent Office Action, the effects of GH on food intake may, at first, appear inconclusive. Some studies show that GH stimulates food intake [6], whereas other show a more or less opposite effect [7]. It has been suggested that species differences may be the main explanation to these seemingly contradictory results. This might be the case with data from non-mammal species like chickens due to a different neuro-endocrine regulation of food intake [8]. However, the different effects of GH on food intake observed within or between mammalian species can be explained by differences in body composition.

It will be clear to one skilled in this field that this phenomenon is, in fact, reflected in the subject application. For example, the data reflected in Examples 1, 2, and 3 of the subject application clearly demonstrates that GH reduces food intake in an obese female Wistar rat model (see, e.g., paragraphs 0084, 0089, and 0101 of the published version of the application (US Patent Publication No. 20050171003)). Paragraph 0009 of the subject application reflects the fact that previous studies involving GH either showed no effect or showed that food intake was increased. The fact that these previously studied mammals were *non-obese* mammals is reflected in, e.g., paragraph 0010, which concludes that a discovery important to the invention is the finding that growth hormone "*is able to induce satiety, or ... has a significant appetite reducing effect, in obese [mature] mammals.*"

The references cited by the Examiner as showing an increase in appetite upon GH administration also involve studies using *non-obese* mammals. Azain et al. [6] involves a study with non-obese female Sprague-Dawley rats (~7% body fat). Rats of this size are generally considered non-obese or even "lean" and are obviously quite different from those employed in the work described in the present application, which have a body fat content of approximately 45%.

Klindt et al. [7] employed young growing pigs that were slaughtered prematurely at a live weight of only 50-57 kg instead of a normal slaughter weight of 90-110 kg. For this reason it can, on good grounds, be anticipated that they were non-obese and therefore did not respond with a reduction of food intake. Further evidence that the degree of adiposity at initiation of GH treatment is the main determinant for which effect GH will have on food intake in humans as in appropriate rat models is presented below.

5. Additional pre-clinical studies evidence the operability of the claimed invention.

Two additional studies have been performed to support enablement of the invention. One of these studies was performed in obese rats and the other study was performed in young rats.

Experimental procedures of the complementary study in obese rats (Fig. 1A)

The experimental outline of this study was very similar that used in the studies described in the patent application. At an age of about 15 months female Wistar rats (Taconic,

Denmark) received a high fat (HF) diet for 12 weeks before start of dosing. The total daily dose (4 mg/kg) of recombinant human growth hormone (Norditropin®, Novo Nordisk, Denmark) was divided in two equal parts which were given at 7.00 a.m. and 2.00 p.m. Food intake was registered on a daily basis.

Experimental procedures of the complementary study in non-obese rats (Fig. 1B)

At an age of about 2 months female Wistar rats (Taconic, Denmark) received a high fat (HF) diet for 12 weeks before start of dosing. The total daily dose (4 mg/kg) of recombinant human growth hormone (Norditropin, Novo Nordisk, Denmark) was divided in two equal parts which were given at 7.00 a.m. and 2.00 p.m. Food intake was registered on a daily basis.

Results of complementary studies

Figure 1A (below) presents further evidence for an appetite-suppressive effect of GH in obese rats with an initial high body fat content (≈45 %). In the same figure (1A) it can also be seen that the inhibition of food intake successively declines as administration of GH continues. Towards the end of the administration period even a slight stimulation of food intake can be observed. These dynamic changes are paralleled by a successive decline in body fat. By the end of the study this process has resulted in massive reduction of body fat, as demonstrated in Table 6 of the application.

GH reduces food intake in situations where an abundance of calories is liberated from endogenous body fat stores, whereas the opposite is true in situations where body fat stores are small and the protein anabolic action of the hormone calls for increased supply of dietary energy. From this it can be predicted that GH will stimulate food (energy) intake in lean rats with a high potential for protein accretion. This is exactly what is seen in figure 1B below. Here, young lean (≈10% body fat) rats of the same gender and strain as the obese animals of figure 1A respond with a prompt increase in food intake. A further illustration of this principle is found in the studies of Azain et al [6], where rats with a body fat content of about 7% were found to increase their food intake in response to GH.

FIGURE 1

A B

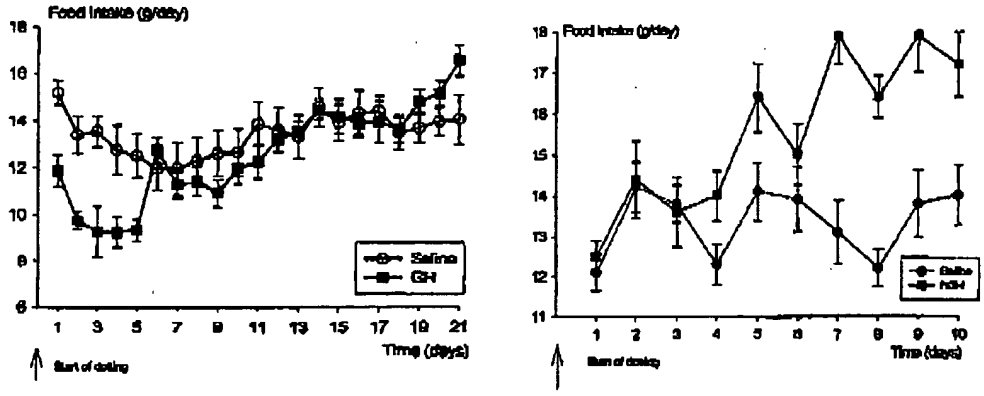

Fig. 1 - Effects of GH on food intake in obese (A, ≈45% body fat) and (B) lean (B, ≈11% body fat) female Wistar rats

Conclusions

The data presented in fig. 1 further demonstrate that the main factor determining the effect of GH on food intake is degree of obesity. This additional information evidences that a scientist or practitioner of ordinary skill will be able to use the claimed method in suppressing appetite in an obese human.

Truthfulness of this Declaration. I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 2007-03-15

Kjell Malmlöf, Ph.D.

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Curriculum Vitæ

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Education and academic appointments

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2000 Associate Professor in Pharmacology, Uppsala University, Uppsala Sweden

Employments

1979-1987	Research and teaching associate Departments of Animal Physiology and Animal Nutrition Swedish Univ. Agric. Sci, Uppsala, Sweden
1987-1990	Research Scientist/Section leader Section of Metabolism, Department of Animal Nutrition Swedish Univ. Agric. Sci, Uppsala, Sweden
(1989-1990	Visiting Scientist, Department of Nutrition INRA, Jouy-en-Josas, France)
1990-1995	Research Scientist/Section leader, Section of Experimental Biology, Department of Pharmacology Peptide Hormones, Pharmacia, Stockholm, Sweden
1995-1996	Clinical Research Manager/Medical writer Medical Department, Peptide Hormones, Pharmacia, Stockholm, Sweden
1996-2003	Research Scientist/Group leader. Pharmacological Research Pharmacology Research and Development, Novo Nordisk, Gentofte and Måløv, Denmark
2003	Principal Scientist/Group leader Pharmacological Research 1 Pharmacology Research and Development, Novo Nordisk Måløv, Denmark

Scientific Societies Membership

North American Association for the Study of Obesity
Growth Hormone Research Society

Referee

European Journal of Pharmaceutical Sciences
Expert opinion on therapeutic patents
Elsevier, Science and Technology
BMC Complementary and Alternative Medicine

Initiator and advisor of PhD projects

Dynamics of adipose tissue metabolism: effects of pharmacological intervention
Signe Mølhøj Jensen, started 2005-03-01

Growth hormone in obesity: An experimental study of effects on lipolysis, body composition and insulin sensitivity,
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Growth Hormone and Insulin-like Growth factor-I during the peri-natal period.
Karin Fhölenhag, Thesis defended in 1997 at the Department of Pharmaceutical Biosciences, Uppsala University

Opponent and examiner

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Medical Faculty, University of Copenhagen, Copenhagen Denmark

Reports and publications

Patents

Published

Arrhenius-Nyberg V, Malmlöf K, Skottner A (1998).Use of insulin and IGF-1
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2003 Obesity and related disorders Smi's conferences, London. UK
2000 "82th Annal meeting endocrine society" Toronto, Canada
2000 "11th International congress of endocrinolog,y ICE2000" Sydney, Australia
2000 "Growth hormone research society conference", Gothenburg Sweden
1998 "80th Annual meeting, endocrine society" New Orleans, USA
1998 "Growth hormone research society conference", San Franscisco, USA.
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